REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-42, 53-63 and 65-70 are pending. Non-elected claims 43-52 were withdrawn from consideration by the Examiner. Applicants have canceled the non-elected claims without prejudice to future prosecution of that subject matter. Similarly, claim 64 has been canceled without prejudice to future prosecution of that subject matter (e.g., Appln. No. 09/545,417).

The priority claim in the specification has been amended to update the status of prior Appln. No. 08/896,085 and to conform with the declaration submitted on October 10, 2001. Issuance of a corrected Official filing receipt will be requested because the filing receipt mailed February 26, 2002 is incorrect.

Amended claim 1 is supported by page 17, line 24, of the specification. Claims 1 and 58 were amended in response to the Examiner's restriction requirement, which restricted the examined subject matter to antigens derived from a pathogen. New claim 70 is directed to the formulation per se. The claim amendments were not required for patentability.

The amendments are supported by the original disclosure and, thus, no new matter has been added. If the Examiner should disagree, however, he is respectfully requested to point out the challenged limitation with particularity in the next Action so support may be cited in response.

In Paper No. 19, the Examiner stated that references listed on Applicants' Form PTO-1449 were missing. Applicants have provided the Examiner with a complete set of references to use in this and other applications. Therefore, the Examiner is requested to consider the listed references and to return an initialed copy of the Form PTO-1440 which was submitted on June 4, 2001.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up

assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1-42 and 53-69 were rejected under Section 112, first paragraph. Applicants traverse. While the Examiner admits that the specification is enabling for "a method for transcutaneous immunization (TCI) comprising applying a formulation that does not include a heterologous adjuvant to intact skin, said formulation consisting of cholera toxin (CT), LT, or *Pseudomonas exotoxin* A (ETA), to hydrated skin," he alleges the specification "does not reasonably provide enablement for,

A) a method for TCI comprising applying a formulation comprised of an antigen, wherein said formulation does not include a heterologous adjuvant to intact skin,

B) a method for TCI comprising activating at least one antigen presenting cell underlying where the formulation's site of application,

C) a method for TCI comprising an APC wherein the APC is a Langerhans cell,

D) a method for TCI comprising applying an antigen in whole cell form,

E) a method for TCI comprising applying an antigen comprising a viral particle or virion,

F) a method for TCI comprising applying diphtheria toxin (DT),

G) a method for TCI wherein the induced immune response recognizes a lipopolysaccharide (LPS).

H) a method for TCI wherein the induced response recognizes influenza virus hemagglutinin (HA), influenza virus nucleoprotein (NP), *Hemophilus influenza* B polysaccharide conjugate (Hib-PS), and *Escherichia coli* colonization factor CS6.

I) a method for TCI wherein underlying endosomes or lysosomes are lysed."

The claimed invention is directed to transcutaneous immunization with antigen which is sufficiently immunogenic that adjuvant is not needed or with a molecule that includes both antigen and adjuvant activities. Molecules which do not require "heterologous adjuvant" include ADP-ribosylating exotoxins, pathogen associated molecular patterns (PAMPs), and cytokines Of course, as taught by the specification and exemplified, there are also antigens that require adjuvant activity to induce an antigen-specific immune response by transcutaneous immunization: diphtheria toxoid (DT),

tetanus toxoid (TT), and CS6. Therefore, using the guidance provided in Applicants' specification, it would not require undue experimentation to determine whether an antigen was sufficiently antigenic to not require an adjuvant or a molecule included both antigen and adjuvant activities.

As an initial matter, Applicants note that the objections quoted above are mostly directed to the lack of working examples for limitations recited in dependent claims. But such examples have already been disclosed in previously-filed application which were incorporated by reference in this specification. No evidence has been cited in the Office Action to contradict the teachings in Applicants' specification or the mechanisms which may be operative in transcutaneous immunization. For example, related applications which are relied upon for priority demonstrate the usefulness of various formulations for transcutaneous immunization (see the first paragraph on page 1 of the specification). As noted above, formulations including an ADP-ribosylating exotoxin, a pathogen associated molecular pattern (PAMP), or a cytokine have been successfully used in transcutaneous immunization and a mechanism for inducing an immune response by activating dendritic cells of the skin which act as antigen presenting cells (e.g., the dendritic cell may be a Langerhans cell underlying the formulation's site of application and be activated by transcutaneous immunization) are shown in working examples of the previously-filed applications. Examples 17-18 support these teachings and are not inconsistent with them. Despite the skepticism expressed on pages 4-5 of the Office Action, no evidence is provided to contradict activation of Langerhans cells as shown by increased MHC Class II and change in cell morphology.

The lysis of endosomes and lysosomes with lytic agents is taught on page 7, line 25, to page 8, line 4, and page 15, lines 9-24, of the specification. For example, a fusogenic fragment of influenza hemagglutinin may be used for lysis of at least some endosomes or lysosomes. No evidence has been cited in the Office Action to contradict this teaching of Applicants' specification.

With regard to the use of antigen in whole cell form or as a viral particle or virion, it is not correct that applying the formulation epicutaneously to skin of an organism without penetrating the skin's dermis layer (claim 1) is not sufficient to bring the antigen in contact with cells in the skin that would initiate an immune response. For example,

physical or chemical penetration may be used to enhance the induction of an immune response by whole virus or bacterium by exposing the stratum corneum. But even large biomolecules like nucleic acids are able to induce an immune response when applied to skin which has not been pretreated other than by hydration.

The weight of evidence in support of the enabling nature of the disclosure of the specification is firmly in favor of the conclusion that undue experimentation would not be needed to practice the present invention and that the enablement rejections are not supported by any factual evidence.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 112 – Written Description

Claim 58 was rejected under Section 112, first paragraph, as allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention." Applicants traverse.

The Examiner alleges, "There is insufficient written description to show that Applicant was in possession of a conjugate comprising an antigen and a heterologous molecule which targets an antigen presenting cell." But Applicants' specification teaches the physical and chemical composition of such conjugates on page 13, line 8, to page 15, line 8. A variety of known targeting molecules are described to form a conjugate with the antigen. They represent a representative number of species within the genus. The conjugate is also described in light of the definitions on page 19, line 26, to page 21, line 16, of the specification.

Withdrawal of the written description rejection made under Section 112, first paragraph, is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention.

35 U.S.C. 112 – Definiteness

Claim 10 was rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse because the claim dependency has been corrected to make clear that the skin is being hydrated.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

Double Patenting

Claim 64 was provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 6 of copending Appln. No. 09/545,417. Applicants traverse because claim 64 has been canceled.

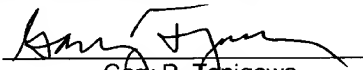
Withdrawal of the double patenting rejection is requested.

Conclusion

Having fully responded to all of the pending objection and rejections of the Office Action (Paper No. 19), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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APPENDIX

MARKED-UP VERSION TO SHOW CHANGES

IN THE SPECIFICATION

The specification is amended as follows.

Page 1, first paragraph starting on line 4,

This application is a continuation-in-part of U.S. Appln. No. 08/896,085 (filed July 17, 1997, now U.S. Patent No. 5,980,898 [and pending]); which is a continuation-in-part of U.S. Appln. No. 08/749,164 (filed November 14, 1996, now U.S. Patent [Pat.] No. 5,910,306); [which is] a continuation-in-part of U.S. Appln. No. 09/257,188 (filed February 25, 1999 and pending); [which is] a continuation-in-part of U.S. Appln. No. 09/309,881 (filed May 11, 1999 and pending); and [which is] a continuation-in-part of U.S. Appln. No. 09/311,720 (filed M[m]ay 14, 1999 and pending); which is a continuation in-part of Intl. Appln. No. PCT/US97/21324 (filed November 14, 1997 designating the U.S., now abandoned).

Page 1, second paragraph starting on line 11,

This application also claims priority benefit from provisional U.S. Appln. No. 60/090,169 (filed June 22, 1998) [and U.S. Appln. No. 60/128,370 (filed April 8, 1999)].

IN THE CLAIMS

The claims are amended as follows.

1. (Amended) A method for transcutaneous immunization comprising:

(a) providing a formulation comprised of at least one molecule which is an antigen derived from a pathogen [or a polynucleotide encoding said antigen], wherein said formulation does not include heterologous adjuvant;

(b) applying said formulation epicutaneously to skin of an organism without penetrating said skin's dermis layer; and

(c) inducing an antigen-specific immune response in said organism, wherein at least one epitope of said antigen is recognized.

10. (Amended) A method of claim 9 [7], wherein hydration enhances the antigen-specific immune response as compared to application of the formulation without hydration.

58. (Amended) A method of claim 1, wherein the antigen [or polynucleotide encoding the antigen] is conjugated to a heterologous molecule which targets an antigen presenting cell.

Claims 43-52 and 64 are canceled without prejudice or disclaimer.

Claim 70 is added as a new claim.